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Musashi-2 (MSI2) supports TGF-β signaling and inhibits claudins to promote non-small cell lung cancer (NSCLC) metastasis

Kudinov A., Deneka A., Nikonova A., Beck T., Ahn Y., Liu X., Martinez C., Schultz F., Reynolds S., Yang D., Cai K., Yaghmour K., Baker K., Egleston B., Nicolas E., Chikwem A., Andrianov G., Singh S., Borghaei H., Serebriiskii I., Gibbons D., Kurie J., Golemis E., Boumber Y.
Kazan Federal University, 420008, Kremlevskaya 18, Kazan, Russia

Abstract

© 2016, National Academy of Sciences. All rights reserved.Non-small cell lung cancer (NSCLC) has a 5-y survival rate of ∼16%, with most deaths associated with uncontrolled metastasis. We screened for stem cell identity-related genes preferentially expressed in a panel of cell lines with high versus low metastatic potential, derived from NSCLC tumors of KrasLA1/+;P53R172HΔG/+ (KP) mice. The Musashi-2 (MSI2) protein, a regulator of mRNA translation, was consistently elevated in metastasis-competent cell lines. MSI2 was overexpressed in 123 human NSCLC tumor specimens versus normal lung, whereas higher expression was associated with disease progression in an independent set of matched normal/primary tumor/lymph node specimens. Depletion of MSI2 in multiple independent metastatic murine and human NSCLC cell lines reduced invasion and metastatic potential, independent of an effect on proliferation. MSI2 depletion significantly induced expression of proteins associated with epithelial identity, including tight junction proteins [claudin 3 (CLDN3), claudin 5 (CLDN5), and claudin 7 (CLDN7)] and down-regulated direct translational targets associated with epithelial-mesenchymal transition, including the TGF-β receptor 1 (TGFβR1), the small mothers against decapentaplegic homolog 3 (SMAD3), and the zinc finger proteins SNAI1 (SNAIL) and SNAI2 (SLUG). Overexpression of TGFβRI reversed the loss of invasion associated with MSI2 depletion, whereas overexpression of CLDN7 inhibited MSI2-dependent invasion. Unexpectedly, MSI2 depletion reduced E-cadherin expression, reflecting a mixed epithelial-mesenchymal phenotype. Based on this work, we propose that MSI2 provides essential support for TGFβR1/SMAD3 signaling and contributes to invasive adenocarcinoma of the lung and may serve as a predictive biomarker of NSCLC aggressiveness.

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Keywords

Claudins, Lung cancer, Metastasis, MSI2, NSCLC